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## Original article

## Predictive value of functional limitation for disease severity in patients with mild chronic heart failure

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## ABSTRACT

**Background:** We aimed to verify a measure for functional limitation using the Performance Measure for Activity of Daily Living-8 (PMADL-8) clinical assessment tool. This tool was utilized to determine disease severity by comparing disease severity with physiological and demographic variables, which have been well documented as predictors for mortality and rehospitalization in chronic heart failure (CHF) patients. **Methods:** We consecutively enrolled 125 CHF patients with impaired left ventricular systolic function who underwent cardiopulmonary exercise testing in Nagoya University Hospital. We measured PMADL-8, which had a total score that ranged from 8 to 32 points, in which higher scores indicated severe functional limitations to evaluate the patient's functional limitations and evaluate clinical physiologic variables, which were established as prognostic factors of CHF. First, the association between PMADL-8 and other clinical variables was analyzed by correlation coefficients, and then, multivariate regression analysis was performed to select independent correlate factors. Lastly, we identified the optimal PMADL-8 threshold for detecting disease severity by comparing with the threshold for disease severity in selected variables.

**Results:** The PMADL-8 indicated excellent correlation with peak oxygen uptake (peakVO<sub>2</sub>) ( $r = -0.743$ ,  $p < 0.001$ ), and the multivariate regression analysis revealed that peakVO<sub>2</sub> was independently correlated with the PMADL-8 ( $p < 0.001$ ). The optimal PMADL-8 threshold for detecting a peakVO<sub>2</sub> value of 18 ml/min/kg was 18 points. Similarly, a peakVO<sub>2</sub> value of 14 ml/min/kg was 22 points, and a peakVO<sub>2</sub> value of 16 ml/min/kg was 20 points.

**Conclusions:** Our data indicate that functional limitation as evaluated by the PMADL-8 is well correlated with peakVO<sub>2</sub>. PMADL-8 may have potential as a clinical assessment tool to manage disease status in CHF patients.

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## Introduction

Chronic heart failure (CHF) is a systemic and progressive disease characterized by functional limitations in daily activities that are caused by clinical symptoms, shortness of breathing, or fatigability [1]. The New York Heart Association (NYHA) functional class is the most well-known clinical marker for functional limitations in

CHF patients and serves as a predictive marker of hospitalization, disease progression, and mortality [2].

Despite the fact that the functional decline in CHF patients reflects disease progression, evidence of functional limitations as a predictive parameter for disease status has not been demonstrated. This may be, in part, due to the lack of an objective measurement tool to evaluate functional limitations in CHF patients. Several questionnaires have been reported to measure functional limitations in CHF patients [3,4], however, these questionnaires were originally developed to measure health-related quality of life (HRQOL) or health status. The factors of functional limitation that are contained in these questionnaires have not been studied independently from the viewpoint of CHF disease status.

Functional limitations manifest as difficulty in performing daily activities. Functional limitations of CHF mostly arise from a

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combination of physical limitations and symptoms. Furthermore, clinical CHF symptoms are induced by disease-specific central and peripheral abnormalities, such as cardiac dysfunction, hemodynamic abnormalities, skeletal muscle abnormalities, and excessive neurohormonal activation [5,6]. Therefore, a subjective measure of functional limitations in CHF patients has the potential to be a clinical predictor for CHF disease severity. To examine this hypothesis, we developed a self-reported, simple questionnaire known as the Performance Measure for Activities of Daily Living-8 (PMADL-8) to assess functional limitations by measuring the difficulty in performing daily activities based on the Japanese CHF population [7].

In this study, we aimed to verify PMADL-8 as a clinical assessment tool to determine disease severity by comparing the PMADL-8 score with physiological and demographic variables that have been documented as predictors for mortality or rehospitalization in CHF patients.

## Materials and methods

### Study area and population

We studied 125 consecutive CHF patients with dilated cardiomyopathy at Nagoya University Hospital between December 2007 and August 2010. Patients who lacked motivation to participate in this study were excluded. All patients had a normal sinus rhythm and reduced left ventricular ejection fraction less than 50%, and were on optimal pharmacological therapy, according to the current guidelines for the treatment of HF [1]. No patients had implantable cardioverter-defibrillators or pacemakers. Each patient was a stable HF patient, underwent cardiopulmonary exercise testing (CPX), laboratory measurements, and echocardiography and answered a self-reported questionnaire. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine (Approval No. 359), and written informed consent was obtained from all of the study subjects.

### PMADL-8

PMADL-8 is an 8-item, self-administered questionnaire that quantifies functional limitations in activity of daily living for patients with HF. PMADL-8 was measured with a 4-category response scale (i.e., 1 = very easy; 2 = somewhat easy; 3 = somewhat hard; and 4 = very hard), which had a total score that ranged from 8 to 32 points, in which higher scores indicated severe functional limitations. The assessment tool had excellent internal consistency, test–retest reliability and validity of hierarchical scale as assessed by a Rasch scaling analysis in elderly Japanese CHF patients [7]. All participants completed the PMADL-8 assessment independently just before CPX was performed.

### Exercise testing

Each patient underwent CPX at a progressively increasing work rate to maximum tolerance on a cycle ergometer. The test protocol was in accordance with the recommendations of the American College of Sports Medicine (ACSM) [8]. All patients began at 0 W for a 3-min warm-up, which was followed by a 10 W/min ramp increment protocol up to the termination criteria [9]. The test termination criteria were determined according to the ACSM criteria. A qualified exercise physiologist conducted each test with a physician's supervision. A 12-lead electrocardiogram was monitored continuously, and blood pressure was measured every minute during exercise and throughout the recovery period. Respiratory gas exchange variables, including oxygen uptake ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ), and minute ventilation (VE), were

acquired continuously throughout the exercise testing using an Ergospirometry Oxycon Pro (Care Fusion; San Diego, CA, USA), and gas-exchange data were obtained with each breath. Peak oxygen uptake ( $\text{peakVO}_2$ ) and the minute ventilation/carbon dioxide production slope ( $\text{VE}/\text{VCO}_2$  slope) were measured as indices of physiologic outcome. The exercise physiologist was blinded to the PMADL-8 scores.

According to American Thoracic Society guideline, the 6-min walking test was performed indoors along a flat, 100-m circular corridor that had a hard surface [10].

### Other parameter measurements

We evaluated other prognostic variables to verify the validity of PMADL-8 as a disease assessment tool. We selected established prognostic variables, including body mass index, plasma brain natriuretic peptide level, serum hemoglobin, serum albumin, and estimated glomerular filtration rate from the results of a blood investigation [11,12], and we obtained the left ventricular ejection fraction (LVEF),  $E/E_a$  which was the ratio of the early transmitral flow velocity to the early diastolic mitral annular velocity from echocardiography findings. Handgrip strength was measured using a Jamar dynamometer. The participants were asked to sit with their wrist in a neutral position and elbow flexed to 90° [13]. Grip strength was measured 3 times for each hand, and the highest value was used for the analysis. Knee extensor muscle strength was measured using a digital hand-held dynamometer (m-Tas F1, Anima Co., Chofu, Tokyo, Japan), which has been validated and shown to be reliable among the elderly [14,15]. During testing, the participant adopted a dangling position with the arms held on the edge of the table and was then fitted with a hand-held dynamometer on the anterior aspect of the measured ankle, which was fixed to the table leg by a vinyl strap. The participants were asked to extend their leg and push with maximal effort 2 times per leg. The lever length was also measured from the lateral joint space of the knee to the lateral top of the belt. The best performance was used as the maximal power and was transformed into Newton meters (Nm).

### Statistical analysis

The data are presented as the mean  $\pm$  standard deviation for the continuous variables and percentages for the categorical data. First, the association between PMADL-8 scores and the clinical variables were analyzed by Pearson's or Spearman's correlation coefficients. Variables with a  $p$ -value less than 0.1 upon univariate analysis were entered into the multivariate regression analysis with a stepwise forward selection procedure to determine the independent factors of PMADL-8. We then identified the optimal PMADL-8 threshold for detecting disease prognosis by comparing with selected variables. All analyses were performed with the SPSS 16.0 software package (SPSS Inc., Tokyo, Japan). A  $p$ -value of less than 0.05 was considered statistically significant.

## Results

The baseline clinical patient characteristics are shown in Table 1. The mean age was 57.6 years (range, 22–86 years) old, and 92% of the patients were classified as NYHA functional class I or II and had mild symptoms. The mean LVEF was 36.4% and 102 patients (81.6%) had reduced LVEF which was less than 40%. Seventy-six patients (64.0%) had been treated with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers because some patients started these medications after examination. No patients had abnormal respiratory function or severe pulmonary hypertension.

**Table 1**  
Patient demographics and clinical characteristics.

	Total (n = 125)
Age (yo)	56.8 (14.1)
Male gender (%)	63
BMI (kg/m <sup>2</sup> )	23.6 (5.3)
PMADL-8	18.8 (5.7)
PeakVO <sub>2</sub> (ml/min/kg)	18.1 (5.4)
VE/VCO <sub>2</sub> -slope	33.2 (9.9)
LVEF (%)	32.4 (8.2)
E/E <sub>a</sub>	15.2 (9.7)
Plasma BNP (pg/ml)	222 (300)
Serum Na (mequiv./l)	139 (2.9)
Hb (g/dl)	13.7 (1.8)
Alb (g/dl)	3.9 (0.4)
e-GFR (ml/min/1.73 m <sup>2</sup> )	63.9 (25.4)
6MD (m)	479 (102)
Medication n (%)	
ACEi/ARB	78 (62.4)
Beta blockers	89 (71.5)
Diuretics	89 (71.5)
Digitalis	44 (35.2)

The data are presented as the mean (standard deviation).

BMI, body mass index; PMADL-8, Performance Measure for Activity of Daily Living-8; peakVO<sub>2</sub>, peak oxygen uptake; VE/VCO<sub>2</sub> slope, minute ventilation/carbon dioxide production; LVEF, left ventricular ejection fraction; E/E<sub>a</sub>, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; BNP, brain natriuretic peptide; serum Na, serum sodium; Hb, hemoglobin; Alb, albumin; eGFR, estimated glomerular filtration rate; 6MD, 6-min walking distance; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker.

**Table 2**  
The correlations between physiological and demographic variables and PMADL-8.

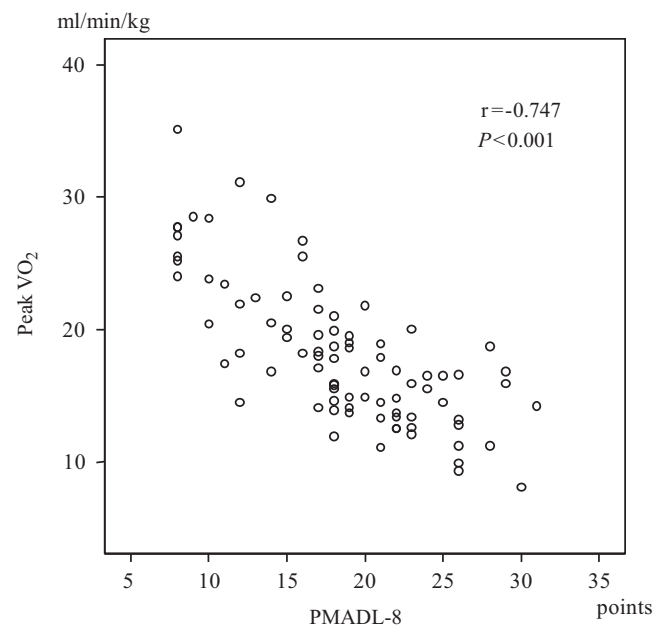
	r	p
Age	0.221	0.042
BMI	0.140	0.198
PeakVO <sub>2</sub>	−0.747	<0.001
VE/VCO <sub>2</sub> -slope	0.357	<0.001
LVEF	−0.135	0.219
E/E <sub>a</sub>	0.221	0.059
Hb	−0.325	0.002
Plasma BNP	0.205	0.067
Alb	−0.211	0.064
eGFR	−0.093	0.483
6MD	−0.557	<0.001
Grip	−0.319	0.007
Leg strength	−0.024	0.048

PMADL-8, Performance Measure for Activity of Daily Living-8; BMI, body mass index; peakVO<sub>2</sub>, peak oxygen uptake; VE/VCO<sub>2</sub> slope, minute ventilation/carbon dioxide production; LVEF, left ventricular ejection fraction; E/E<sub>a</sub>, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; Hb, hemoglobin; BNP, brain natriuretic peptide; Alb, albumin; eGFR, estimated glomerular filtration rate; and 6MD, 6-min walking distance.

The correlations between the PMADL-8 score and the other clinical parameters are presented in Table 2 and Fig. 1. Age, peakVO<sub>2</sub>, VE/VCO<sub>2</sub>-slope, hemoglobin, plasma BNP level, 6-min walking distance, grip strength, and knee extensor muscle strength were significantly correlated with PMADL-8 score, whereas LVEF was not. The result of multivariate linear regression analysis revealed that peakVO<sub>2</sub> was an independently correlated factor of the PMADL-8 score ( $r = 0.635$ ,  $p < 0.001$ ). An estimated regression equation is displayed in Table 3. After calculations using this equation, the optimal PMADL-8 threshold predicting 18 ml/min/kg of peakVO<sub>2</sub> was 18 points. Similarly, a peakVO<sub>2</sub> value at 14 ml/min/kg was 22 points, and a peakVO<sub>2</sub> value at 16 ml/min/kg was 20 points.

## Discussion

The main finding of this study was that, in stable CHF patients, the PMADL-8 score was closely correlated to the peakVO<sub>2</sub> value.

**Fig. 1.** Correlation between PMADL-8 and peakVO<sub>2</sub>. PMADL-8 was significantly correlated with peakVO<sub>2</sub>. PMADL-8, Performance Measure for Activity of Daily Living-8; peakVO<sub>2</sub>, peak oxygen uptake.

The results of this study suggest that PMADL-8 is a useful assessment tool for measuring disease severity in stable systolic HF patients.

The results of this study clarify that the PMADL-8 score is a valid assessment tool for measuring CHF disease severity, and summary scores of 18 and 22 are meaningful thresholds for evaluating CHF disease severity. In previous research concerning CHF disease-specific self-reporting questionnaires, such as the Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure questionnaire, were developed for evaluating HRQOL and included more than 20 items. Other questionnaires, such as the Specific Activity Scale and the Left Ventricular Dysfunction 36, were also developed for evaluating activity in CHF patients. These questionnaires evaluated the multidimensional aspects of CHF patients, which included physical limitations, symptoms, self-efficacy, and social interference, and these questionnaires independently associated with peakVO<sub>2</sub> values ( $r = 0.3$ – $0.6$ ) [3,4,16–18]. In contrast, PMADL-8 is a single-dimensional questionnaire that focuses on functional limitations in activity of daily living of CHF patients [7], and the study results demonstrate an excellent correlation with peakVO<sub>2</sub> values that support assessment tool validity.

**Table 3**  
Multivariate regression analysis results.

	B	SE	B (95% CI)		p
			Min	Max	
PeakVO <sub>2</sub>	−0.878	0.182	−4.581	−0.635	<0.001
	34.31	3.230			<0.001

$R = 0.635$ ,  $R^2 = 0.420$ ,  $p < 0.001$ .

Estimated regression equation: PMADL-8 score =  $-0.878 \times \text{peakVO}_2 \text{ value} + 34.31$ .  
Dependent variable: PMADL-8.

Independent variables: age, peakVO<sub>2</sub>, VE/VCO<sub>2</sub>-slope, LVEF, E/E<sub>a</sub>, Hb, BNP, Alb, 6MD. PMADL-8, Performance Measure for Activity of Daily Living-8; peakVO<sub>2</sub>, peak oxygen uptake; VE/VCO<sub>2</sub> slope, minute ventilation/carbon dioxide production; LVEF, left ventricular ejection fraction; E/E<sub>a</sub>, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; Hb, hemoglobin; BNP, brain natriuretic peptide; Alb, albumin; 6MD, 6-min walking distance.

The functional limitations in CHF primarily manifest from clinical symptoms, which are due to not only left ventricular dysfunction but also systemic factors, such as skeletal muscle dysfunction [5], autonomic nervous system abnormalities [19] and excessive neurohormonal activation [6]. Even the main symptoms of fatigability and dyspnea are hypothesized to be induced by skeletal myopathy and muscle ergoreflex abnormalities [20]. Thus, the functional limitations described in PMADL-8 appear to reflect central and systemic disease-specific abnormalities in CHF patients.

The findings of our study provide us the meanings of PMADL-8 score with CHF disease severity. The findings indicate that a PMADL-8 score of 18 reflects a peakVO<sub>2</sub> value of 18 ml/min/kg; similarly, a PMADL-8 score of 22 reflects a peakVO<sub>2</sub> value of 14 ml/min/kg. A peakVO<sub>2</sub> value of 18 ml/min/kg was suggested to be a threshold for difficulty in ADL among community-dwelling elderly people [21] and poor prognosis in CHF patients [22] and the healthy elderly [23]. A peakVO<sub>2</sub> value of 14 ml/min/kg, which indicated a very poor prognosis in CHF patients [22], has been applied as a criterion for cardiac transplantation [1]. Specifically, a PMADL-8 score greater than 18 points indicated that the patient selected 3 = somewhat hard for two or more items and that the patient had begun to feel some difficulty in daily life. Because atrial fibrillation (Af) is one confounding factor of echocardiography findings, patients with Af were excluded in this study. However, we also confirmed that there was a good correlation between PMADL-8 and peakVO<sub>2</sub> in another group of 18 patients with chronic Af ( $r = -0.733$ ,  $p < 0.001$ , data not shown). Therefore, PMADL-8 may be also useful for HF patients with Af.

ACC/AHA guidelines [1] provide few tools for monitoring CHF patients. Although many clinical markers, such as echocardiography, electrocardiography, hemodynamic status, biochemical and exercise testing, have been provided for CHF risk stratification, some of these tend to be invasive, complicated to obtain, and costly. In contrast, PMADL-8 is simple to administrate and score, is noninvasive, and can be administrated repeatedly at a low cost. PMADL-8 may have an important role in clinical research and disease management programs in which follow-up and care need to be efficiently provided for an entire population of CHF patients.

This study has potential limitations. Our patients had mild to moderate CHF, and it remains unclear whether PMADL-8 is also correlated with peakVO<sub>2</sub> among patients with moderate to severe CHF. However, it is contraindicated to perform CPX in CHF patients with NYHA class IV, so PMADL-8 may serve as meaningful information on CHF outpatients. This study was determined by cross-sectional assessment, therefore, we cannot describe the association between changes in PMADL-8 and changes in peakVO<sub>2</sub>, so further research is needed to confirm the responsiveness of PMADL-8. Furthermore, the association PMADL-8 score and clinical hard endpoints also remain unclear. These shortcomings will be addressed by the results of our ongoing, prospective study “PTMaTCH” (Preventive effect of exercise for management of daily functioning in patients with CHF: a rehabilitation cohort study) in which we will analyze the relationship between the time between the PMADL-8 assessment after discharge and rehospitalization in CHF patients who were hospitalized due to an acute exacerbation. Nevertheless, the results of the present study provide novel information that functional limitation will be a possible clinical assessment tool to determine disease severity in CHF patients. Further study will be required to investigate the responsiveness of PMADL-8 in high-risk CHF patients.

## Conclusions

The findings of the present study indicate that the PMADL-8 score is closely correlated with peak oxygen uptake. PMADL-8 is

a simple and inexpensive tool for evaluating functional limitation and may provide a meaningful outcome in cardiovascular rehabilitation as well as clinical epidemiological research for patients with CHF.

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## Appendix A.

### Performance Measure for Activities of Daily Living-8 (PMADL-8)

1 = very easy; 2 = somewhat easy; 3 = somewhat hard; and 4 = very hard

1.	Getting up and off from the floor without tools
2.	Washing your body and hair
3.	Walking upstairs without a handrail
4.	Vacuuming your room
5.	Pulling and closing a heavy sliding door
6.	Getting into and out of a car
7.	Walking at the same speed with someone of the same age
8.	Walking up a slight slope for 10 min

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